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LETTER FROM MOBAY CORPORATION TO USEPA SUBMITTING ENCLOSED SUBMISSION ON TOLUENE DIISOCYANATE LONGITUDINAL STUDY OF RESPIRATORY HAZARDS IN POLYURETHANE FOAM WITH ATTACHMENT		
Chemical Category		
TOLUENE DIISOCYANATE (26471-62-5)		

CONTAINS NO CBI

Mobay



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A Bayer USA INC COMPANY

Mobay Corporation
Health, Environment, Safety
& Plant Management

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September 17, 1991

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86910001010

Attention: 8(d) Health and Safety Reporting Rule
(Notification/Reporting)



86910001010

Gentlemen:

Enclosed is a copy of a Health and Safety Study.

We are submitting this study on behalf of Mobay Corporation, Mobay Road, Pittsburgh, Pennsylvania 15205. We are filing this Health and Safety Study to comply with the regulations codified at 40 CFR, Part 716. This submission contains no Confidential Business Information (CBI).

The information required at 40 CFR 716.35(b) is:

Chemical Name: Toluene Diisocyanate
CAS No: 26471-62-5
Name of Study: Longitudinal Study of Respiratory Hazards in the
Polyurethane Foaming Industry

Submitting Official: Francis J. Rattay
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Sincerely,

Francis J. Rattay
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Manager, Regulatory Compliance
(412) 777-7471

Attachment
Certified Mail No.: 382 040 026

cc: 8(d) File 91-12-15
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Core Project B: Longitudinal Study of Respiratory Hazards in the Polyurethane Foaming Industry**1. Rationale**

The objective was the assessment of respiratory health of workers exposed to toluene diisocyanate in the production of polyurethane foam. The target study population consisted of all workers employed in two plants of the same company, both producing flexible foam. Concentrations of TDI associated with various jobs and departments in the two plants were measured using personal monitors. There were 507 monitoring runs on 256 workers, resulting (from the sampling "window" of this instrument) in 4,845 intervals of measured personal exposure. Individual work histories were then used to assign cumulative exposure estimates based on time in each job. For some analyses, the subjects were divided into terciles of cumulative exposure. Exposure was also expressed as time above specified concentrations of TDI. Annual change in lung function was the primary response variable. Methacholine reactivity was measured by inhalation challenge testing, and atopy was defined using skin prick testing with common aeroallergens. Total IgE levels and RAST reactivity to a tolyl-isocyanate-HSA conjugate were obtained from sera. Respiratory symptoms and smoking history were obtained using an administered questionnaire. Analyses explored the associations between measures of exposure, outcome variables, and potential influencing and confounding variables.

2. Accomplishments

Following final data collection in Year 6, the data were edited and updated and incorporated into final datasets. Analysis has been essentially completed.

TDI monitoring showed the following percentages of samples (total samples = 4,845) to reflect TDI concentrations above specified levels: 50% were greater than the lower detection limit ("LDL" = .0005 ppm in 1982, .00025 ppm thereafter); 9% exceeded .005 ppm; and 1% exceeded .02 ppm. In 955 samples in the "Foam" job category, the percentages were 68% > LDL, 20% > .005 ppm, and 3% > .02 ppm. Individual cumulative exposure estimates were assigned for three periods: hire to baseline examination (for cross-sectional analysis of baseline data), and baseline to end of study and hire to end of study (used in analyses of longitudinal change).

Table 1 summarizes participation of the 435 workers in the target population. Three hundred eighty six workers (88.7%) were examined at least once in the six years of data collection. Skin testing was done at the initial examination of each subject, and was obtained in 365 persons (84.1%).

The participants (386) included 249 workers in Plant 1 and 137 in Plant 2. Distributions by sex (76% male) and race (77% white, 18% black, 4% Hispanic) were similar in the two plants. Plant 1 is the older plant, and its employees are on average older (39.4 vs. 33.8 yrs)

and have longer work in plant (11.4 vs. 6.0 yr, at study entry) than those in Plant 2. Baseline observations (at time of study entry for each subject) are shown in Table 2.

Cigarette smoking was categorized as current, ex (no regular use for at least one year), or never. Those who smoked only pipes or cigars were placed in the "never" (cigarette) category. Differences in baseline values among smoking categories are shown in Table 3.

Cumulative exposure (hire to baseline) was strongly associated with length of work in the plants (Table 4). Those in the lowest tercile of cumulative exposure had a mean IgE level higher than the others. Those in the highest tercile had significantly lower mean FEF_{25-75} . The expected inverse relationships to exposure are also noted for FEV_1 and FVC, though they are not statistically significant.

Within smoking categories (Table 5), the ordering of mean baseline FEF_{25-75} according to cumulative exposure is seen to occur in the ex- and never-smoking categories.

No significant relationships were found between smoking and atopy, whether defining the latter inclusively (positive skin tests) or restrictively (positive skin tests and personal or family history of atopic disease). By the inclusive definition, 29% (105/365) of those with status determined were atopic. Atopy was not related to exposure indices or lung function.

Methacholine reactivity ($PD_{20}FEV_1$, by dosimeter administration with doubling dose protocol) was associated with significantly lower expiratory flowrates (Table 6).

Multiple regression was used to evaluate the effects of potential influencing variables on baseline lung function. Cumulative exposure (hire to baseline) was expressed as a continuous variable. Smoking was treated as a categorical variable. Table 7 shows the regression coefficients. Thus, an increase in TDI exposure of 0.1 ppm-mo was associated with a reduction of 2.3% in FEF_{25-75} in each smoking category, at the level $p < .063$. For FEV_1 and FVC, significant exposure effects were found only in current smokers, each 0.1 ppm-mo increment being associated with reductions of 4.3 ($p < .00025$) and 4.4% ($p < .00005$), respectively. Adjusting for the other variables shown in Table 7, methacholine reactivity was associated with lower mean (\pm s.e.) FEF_{25-75} %P, (70.98 ± 2.76 , vs. 91.03 ± 1.53).

Only 52% (227/435) of the target population had sufficient data for computation of rates of annual change (hereafter, "slopes") from three or more points. Table 8 compares those with and those without slopes, among the 386 having baseline data. Those with slopes are significantly taller, and have more time in plant and cumulative exposure, than those without slopes. Baseline lung function is virtually identical between the groups. Not shown are other similarities between the slope and baseline populations: percentages of current smokers (35 vs 35), atopics (28 vs. 29), and methacholine reactors (20 vs. 23). The slope population thus appears representative of the baseline population. Mean slopes are not significantly different between plants ($-.063$ vs. $-.055$ L/yr).

Annual change in pulmonary function was studied using a weighted multiple regression followed by a weighted stepwise multiple regression. Several models using various subsets of

independent variables (smoking status, gender, atopy--separate analyses for each definition, methacholine response, cumulative exposure [hire to end of study], IgE, age and appropriate interactions among these variables) were considered in exploratory analyses. The objective was to assess the importance of interactions between main effects and covariates. From these exploratory analyses, a model was developed for final analysis by stepwise multiple regression. Independent variables in this stepwise regression were smoking status, gender, atopy (separate analyses for each definition), methacholine response, cumulative exposure (hire to end of study, considered as a continuous variable), IgE, age, and interactions (atopy with exposure, methacholine response with exposure, gender with age, methacholine response with age, and methacholine response with IgE).

Since results of stepwise regression analyses were similar regardless of the definition of atopy used, stepwise regression analyses were pursued using atopy as defined by skin test data only. Asthmatics (17/227, 7.5%) were deleted from stepwise analyses. An asthmatic was defined as a worker having TDI asthma (six were proven by inhalation challenge) and/or one whose questionnaire indicated a physician's diagnosis of asthma. Models for analysis of annual change in FEV₁ were evaluated under three different conditions: forcing smoking status into the model; forcing smoking status and gender; forcing smoking status, gender and exposure. Coefficients were comparable under the three conditions, so the parsimonious model forcing smoking status was chosen for further examination (Table 9). Neither a smoking effect nor an effect of exposure was noted. Males had a worse adjusted mean annual FEV₁ change, -71 ml/yr, than did females, -43 ml/yr ($p < .0045$). This 27 ml/yr (from the regression coefficient) difference for gender was greater than the 8-11 ml/yr difference usually observed. Methacholine responders had a (marginally significant, $p < .0895$) worse adjusted mean annual FEV₁ change, -66 ml/yr, than did nonresponders, -48 ml/yr.

Table 10 shows mean slopes by smoking category. Despite the lack of significant effect in the regression analysis, the values show the expected ordering by smoking category.

Table 11 shows mean FEV₁ slopes by exposure and smoking category. The lack of exposure effect is evident. There is the expected ordering by smoking category in the low and medium categories, but not in the high category, of cumulative exposure. In light of the strong gender effect, the preceding tabulation was repeated using only the men (Table 12). There is again an expected ordering of mean declines according to smoking, among the less exposed workers.

Because cumulative exposure (hire to end of study) is highly correlated with length of employment, the preceding tabulation was repeated using cumulative exposure during only the 1982-1987 study period (Table 13). This reorders subjects according to exposures only in the study period, and results in relatively even distribution of mean plant employment length among the cumulative (1982-1987) exposure categories. The ordering by smoking categories is not changed; there is still no evidence of an exposure effect.

Since the personal TDI monitors sample over relatively short intervals, the data provide information on exposure excursions ("peaks") as well as time weighted average levels. This was used to express individual exposures as durations spent above two concentrations of TDI,

.005 and .02 ppm. Regression analysis failed to show significant associations between time exposed above these levels and the annual declines in any test of lung function, after controlling for other influencing variables.

The results of the analyses are here summarized, by outcome variables:

- (1) *Baseline lung function*, percent predicted, was significantly related (see Tables 3, 6 and 7) to:
 - (a) smoking: FEF_{25-75} and FEV_1/FVC ;
 - (b) cumulative exposure (hire to baseline): significant effects on FEV_1 and FVC in current smokers, and on FEF_{25-75} across all smoking categories;
 - (c) methacholine responsiveness: FEV_1 , FEV_1/FVC , and FEF_{25-75} ;
 - (d) age: only to FEF_{25-75} .

Baseline function was not related to atopy.

- (2) *Annual change in lung function* was related (see Table 9) to:
 - (a) gender ($p < .0045$): FEV_1 , with a larger than expected adverse effect of male gender, -27 ml/yr;
 - (b) methacholine responsiveness: FEV_1 (at marginal significance, $p < .0895$).

Annual change was not significantly related to either smoking or measures of cumulative exposure. The latter notwithstanding, there is an obvious ordering of mean FEV_1 declines by smoking category (Table 10), and this ordering seems to be found in those with lower cumulative exposure (hire to end of study) (Tables 11 and 12).

The most disturbing finding is the accelerated decline in lung function observed in the entire population. Mean FEV_1 declines of 53 ml/yr in nonsmokers and 67 ml/yr in smokers, in a currently employed population, are very much larger than expected from either the medical literature or our own experience. They are also far larger than the declines observed in a concurrent longitudinal occupational study that we performed with the same equipment, technicians, and testing protocol. In an effort to detect any secular bias, we examined plots of mean FEV_1 level, by year, for those fifty-five subjects who had spirometric data at all six annual visits: there was no aberrant point. We have found no reason to disbelieve the observation of highly abnormal rates of annual decline. Because of the bias of employment, which tends to select healthier individuals, the generally good levels of baseline lung function in terms of general population norms (*i.e.*, in percent predicted) is by no means inconsistent with a valid observation of abnormal rates of decline.

A source of major concern is whether TDI, the workplace pollutant measured in this study, is the only potential respiratory toxin associated with foam production. We and others have been unsuccessful in relating respiratory effects to amine exposures in this environment, but those studies are not definitive. Foam production liberates other volatile chemicals that could

have toxic main effects, or interactions with TDI or smoking. TDI is responsible for most or all of the occupational asthma in this study population, but the abnormal loss of lung function persists when all known asthmatics are eliminated from the analyses.

These findings support a conclusion that polyurethane foam production is associated with a risk of abnormally large decline in lung function. Because various measures of TDI exposure did not correlate with accelerated decline, the question arises whether control of TDI exposures will provide the full measure of respiratory health protection in this industry.

3. Plans for the Coming Year

The work is completed, except for minimal further analyses needed for presentation and publication.

TABLE 1. NUMBERS EXAMINED AT EACH ANNUAL VISIT

	VISIT					
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>
ELIGIBLE	394	397	423	435	*	*
PARTICIPATED IN:						
Interview:	332	231	224	215	ND	ND
Spirometry:	294	218	230	202	150	128
IgE, RAST:	312	222	236	185	146	ND

* No accession after visit 4, because of insufficient followup time.

ND: not done

TABLE 2. BASELINE OBSERVATIONS, BY PLANT

	PLANT 1				PLANT 2		
	N	MEAN	S.E.		N	MEAN	S.E.
Exposure, ppm-mo Hire-baseline	229	0.11	0.01	§	133	0.06	0.00
Exposure, ppm-mo Hire-1987	249	0.13	0.01	*	137	0.10	0.01
IgE, IU/ml	218	114	18		131	132	21.7
RAST, %bound	217	1.25	0.03		131	1.25	0.02
FEV ₁ , %P	231	105.2	1.0		133	107.1	1.0
FEF ₂₅₋₇₅ , %P	231	35.9	1.7		133	29.4	1.9
FVC, %P	231	106.0	0.8		133	105.7	1.0

SIGNIFICANT DIFFERENCE BETWEEN PLANTS: * $p < 0.025$; § $p < 0.001$

TABLE 3. BASELINE VALUES BY SMOKING CATEGORY

VARIABLE	CIGARETTE SMOKING CATEGORY					
	CURRENT (N=126-133)		EX (N=80-85)		NEVER (N=145-157)	
	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.
YRS IN PLANT	* 9.04	0.65	12.52	0.89	8.22	0.59
EXPR, SINCE HIRE ppm-mo	** 0.10	0.01	0.13	0.02	0.06	0.01
IgE*, IU/ml	147	23	91	18	113	24
RAST*, %bound	1.25	0.03	1.25	0.02	1.25	0.03
FEV ₁ , %P	105.1	1.3	104.9	1.7	107.2	1.0
FVC, %P	106.0	1.1	107.0	1.38	106.2	0.9
FEF ₂₅₋₇₅ , %P	† 86.1	2.2	81.7	3.1	90.9	1.8
FEV ₁ /FVC, %P	§ 96.2	0.6	95.1	1.0	98.2	0.5

*ln transformation for analysis

p-values for significance of differences among means: * < .0005, ** < .0001, † < .025, § < .005

TABLE 4. BASELINE VALUES BY EXPOSURE TERCILE

VARIABLE	TERCILE EXPOSURE, HIRE-BASELINE, IN ppm-mo					
	≤ .032 (N=108-120)		> .032, ≤ .086 (N=109-121)		> .086 (N=112-121)	
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.
YRS IN PLANT	* 4.45	0.50	6.34	0.28	17.56	0.55
IgE*, IU/ml	143	35	106	17	105	17
RAST*, %bound	1.23	0.04	1.26	0.02	1.25	0.04
FEV ₁ , %P	107.4	1.1	106.3	1.2	104.2	1.4
FVC, %P	107.7	1.1	106.1	1.0	105.1	1.2
FEF ₂₅₋₇₅ , %P	§ 88.0	2.0	91.0	2.4	82.3	2.3
FEV ₁ /FVC, %P	97.0	0.6	97.0	0.7	96.3	0.7

*ln transformation for analysis

p-values for significance of differences among means: * < .0001, § < .025

TABLE 5. BASELINE LUNG FUNCTION (PERCENT PREDICTED) BY EXPOSURE TERCILE AND SMOKING CATEGORY

SMOKING CATEGORY		EXPOSURE TERCILE (HIRE-BASELINE), ppm-mo					
		$\leq .032$		$> .032, \leq .086$		$> .086$	
		N	MEAN	N	MEAN	N	MEAN
CURRENT	FEV ₁	29	105.8	52	107.4	44	102.3
	FVC		109.8		107.1		102.7
	FEF ₂₅₋₇₅		79.5		92.5		82.6
EX	FEV ₁	19	109.3	22	102.3	39	104.2
	FVC		110.4		105.0		106.5
	FEF ₂₅₋₇₅		86.2		82.5		79.0
NEVER	FEV ₁	71	107.8	47	106.9	38	106.5
	FVC		106.4		105.5		106.4
	FEF ₂₅₋₇₅		92.4		93.4		85.5

TABLE 6. BASELINE LUNG FUNCTION BY METHACHOLINE RESPONSE

TEST	METHACHOLINE RESPONSE: CUMULATIVE BREATH UNITS						
	NEGATIVE: PD ₂₀ FEV ₁ > 320			POSITIVE: PD ₂₀ FEV ₁ ≤ 320			
	N	MEAN	S.E.		N	MEAN	S.E.
FEV ₁ , %P	225	107.9	0.8	*	66	99.6	1.8
FVC, %P	225	107.1	0.8		66	105.0	1.5
FEF ₂₅₋₇₅ , %P	225	91.0	1.4	*	66	71.0	3.1
FEV ₁ /FVC, %P	224	97.9	0.4	*	66	91.7	1.0

* p-values for differences between means: < .0001

TABLE 7. REGRESSION COEFFICIENTS FOR BASELINE LUNG FUNCTION

INTERCEPTS	LUNG FUNCTION, PERCENT PREDICTED					
	FEV ₁		FVC		FEF ₂₅₋₇₅	
CURRENT	108.4		105.8		104.4	
EX	104.2		101.0		106.1	
NEVER	107.3		102.7		107.7	
	COEFF.	p <	COEFF.	p <	COEFF.	p <
EXPOSURE ^a					-2.3	.063
CURRENT	-4.3	.00025	-4.4	.00005		
EX	-.04	.49	0.2	.42		
NEVER	-1.4	.20	-0.8	.29		
ATOPIC ^a	-1.5	.19	-2.2	.07	2.2	.77
METHACHOLINE RESPONSIVE ^b	-8.5	.0001	-2.4	.13	-20.0	.0001
AGE ^a	.09	.15	.17	.98	-0.4	.009

^a EXPOSURE UNIT IS 0.1 ppm-mo ^b 1-TAILED t ^c F-TEST

TABLE 8. BASELINE VALUES FOR THOSE WITH AND WITHOUT SLOPES

	WITH SLOPES				WITHOUT SLOPES		
	N	MEAN	S.E.		N	MEAN	S.E.
AGE	227	37.3	0.6		151	37.5	0.9
HEIGHT	227	68.9	0.2	*	151	67.7	0.3
YEARS IN PLANT	227	9.8	0.5		136	8.8	0.7
EXPOSURE ppm-mo.	226	0.10	0.01		136	0.08	0.01
FEV ₁ , %P	227	106.0	0.9		137	105.8	1.2
FVC, %P	227	106.6	0.8		137	105.6	1.0
FEF ₂₅₋₇₅ , %P	227	86.2	1.5		137	88.7	2.3
FEV ₁ /FVC, %P	227	96.5	0.5		136	97.4	0.6

* p < .0025

TABLE 9. REGRESSION COEFFICIENTS FOR ANNUAL CHANGE IN FEV₁ (ML/YR)

VARIABLE	COEFFICIENT	p VALUE LESS THAN:
SMOKING:		
CURRENT vs NEVER*	-.006	.2599
EX vs NEVER*	-.0003	.4875
MALE GENDER*	-.027	.0045
METHACHOLINE RESPONSIVENESS*	-.017	.0895
CUMULATIVE EXPOSURE*	.029	.7801
AGE (YEARS)*	-.0004	.1845

*1-tailed t *F-test

TABLE 10. MEAN ANNUAL CHANGE BY SMOKING CATEGORY

	SMOKING CATEGORY					
	CURRENT (N=79)		EX (N=48)		NEVER (N=100)	
	MEAN	S.E.	MEAN	S.E.	MEAN	S.E.
FEV ₁ , L/yr	-.067	.009	-.059	.008	-.053	.005
FVC, L/yr	-.066	.009	-.059	.010	-.051	.006
FEF ₂₅₋₇₅ L/sec/yr	-.099	.016	-.071	.018	-.076	.011

TABLE 11. MEAN ANNUAL CHANGE IN FEV₁ (L/YR) BY SMOKING CATEGORY AND CUMULATIVE EXPOSURE TERCILE

EXPOSURE TERCILE (ppm-mo)	SMOKING CATEGORY						
	CURRENT		EX		NEVER		TOTAL
	N	MEAN (S.E.)	N	MEAN (S.E.)	N	MEAN (S.E.)	
≤ .080	21	-.073 (.027)	8	-.069 (.018)	46	-.059 (.007)	-.064 (.009)
> .080, ≤ .154	31	-.066 (.010)	17	-.051 (.012)	28	-.035 (.010)	-.051 (.006)
> .154	27	-.065 (.008)	23	-.061 (.014)	26	-.061 (.010)	-.062 (.006)
TOTAL	79	-.067 (.009)	48	-.059 (.008)	100	-.053 (.005)	-.059 (.004)

 TABLE 12. MEN ONLY: MEAN ANNUAL CHANGE IN FEV₁ (L/YR) BY SMOKING CATEGORY AND EXPOSURE CATEGORY

EXPOSURE CATEGORY	SMOKING CATEGORY						TOTAL
	CURRENT		EX		NEVER		
	N	MEAN (S.E.)	N	MEAN (S.E.)	N	MEAN (S.E.)	
≤ .080	11	-.103 (.047)	6	-.075 (.023)	31	-.058 (.010)	-.070 (.013)
> .080, ≤ .154	22	-.075 (.023)	16	-.052 (.013)	21	-.046 (.011)	-.059 (.007)
> .154	26	-.065 (.009)	23	-.061 (.014)	25	-.063 (.010)	-.063 (.006)
TOTAL	59	-.076 (.010)	45	-.060 (.009)	77	-.055 (.006)	-.064 (.005)

TABLE 13. MEN ONLY: MEAN ANNUAL CHANGE IN FEV₁ (L/YR) BY SMOKING CATEGORY AND EXPOSURE CATEGORY (CUMULATIVE EXPOSURE ONLY IN PERIOD 1982-1987)

EXPOSURE CATEGORY	SMOKING CATEGORY						TOTAL
	CURRENT		EX		NEVER		
	N	MEAN (S.E.)	N	MEAN (S.E.)	N	MEAN (S.E.)	
≤ .031	12	-.079 (.021)	14	-.057 (.016)	25	-.065 (.012)	-.066 (.009)
> .031, ≤ .054	18	-.074 (.029)	14	-.064 (.016)	28	-.051 (.008)	-.061 (.010)
.054	29	-.077 (.008)	17	-.059 (.016)	24	-.054 (.011)	-.065 (.006)
TOTAL	59	-.076 (.010)	45	-.050 (.009)	77	-.056 (.006)	-.064 (.005)

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